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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,283	08/16/2001	Usha Kasid	P 0280652 KAUS430501	9971

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,283	KASID ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/12, 3/4, 5/26 04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed May 26, 2004.

Claim 11 has been canceled. Claims 1-4, 7-9, and 16 have been amended. New claims 28-54 are acknowledged.

Claims 1-10 and 12-54 are pending in the instant application.

Claims 1-10 and 12-54 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statements filed February 12, 2004, March 1, 2004, and May 26, 2004 are acknowledged. It is noted that the information disclosure statements filed February 12, 2004, March 1, 2004 are duplicates of each other. The Examiner has considered the references contained in the information disclosure statements filed February 12, 2004 and May 26, 2004.

Double Patenting

In the previous Office Action mailed February 25, 2004, claims 1-8 and 17 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 8 and 13 of U.S. Patent No. 6,126,965 ('965 patent). Additionally, claims

9, 10, 12-16, and 18-20 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,333,314. **These rejections are maintained** for the reasons of record set forth in the previous Office Action.

Response to Arguments

In response to this rejection, Applicants intend to file Terminal Disclaimers in accordance with 37 C.F.R. §1.321 during the pendency of the instant application.

Applicant's amendment necessitated the new ground(s) of rejection presented below: **These are new rejections**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

New claims 28-41 and 45-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 8 and 13 of U.S. Patent No. 6,126,965 ('965). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions as claimed in the issued '965 patent embraces the species of the instantly claimed compositions. For example, the composition *comprising* a cationic liposome comprising a cationic lipid, phosphatidylcholine and cholesterol, wherein the liposome contains an antisense oligonucleotide, wherein the antisense comprises a sequence of SEQ ID NO:1 or SEQ ID NO:2 of claims 28-41 and 45-54 of the instant claims overlaps in scope with the patented claims, composition comprising cationic liposomes which consist essentially of phosphatidylcholine and cholesterol, further comprising dimethyldioctadecyl ammonium bromide (DDAB) and further having encapsulated at least one modified oligonucleotide (claim 1); and wherein said oligonucleotide is SEQ ID NO:1 or SEQ ID NO:2 (claim 6); and further comprising a pharmaceutically acceptable carrier (claim 8) of '965. Therefore the compositions as claimed in the '965 patent would be a species of the instantly claimed compositions.

New claims 42-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,333,314 ('314). Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods as claimed in the issued '314 patent embraces the species of the instantly

claimed methods. For example, the method of radiosensitizing tumor tissue by administering an antisense oligonucleotide contained within a liposome comprising a nontoxic cationic lipid containing SEQ ID NO:1, claim 41 or SEQ ID NO:2, claims 43 and 44 of the instant claims overlaps in scope with the patented claims, the method of radiosensitizing tumor tissue by administering a composition comprising a cationic liposome, phosphatidylcholine and cholesterol, and further comprising a radiosensitizing encapsulated antisense oligonucleotide containing SEQ ID NO:1 (claim 1), wherein the oligonucleotide is phosphorothioated at the end nucleotides (claim 2 or 6) of '314. Therefore the methods as claimed in the '314 patent would be a species of the instantly claimed methods.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed February 25, 2004, claims 18-27 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an improved method of treating a patient having cancerous tumor tissue, comprising the administration of therapeutic radiation, wherein the improvement comprises sensitizing said cancerous tumor tissue by administration of a composition comprising a cationic liposome, phosphatidylcholine, and cholesterol, and further comprises an encapsulated antisense oligonucleotide of no more than 40 bases containing SEQ ID NO:1, does not reasonably provide enablement for an improved method of treating a patient having cancerous tumor tissue comprising the administration of therapeutic radiation wherein the improvement comprises sensitizing said cancerous tumor tissue by the administration of a radiosensitizing composition comprising a cationic liposome, phosphatidylcholine, and cholesterol, and further comprises any

encapsulated oncogene antisense oligonucleotide of no more than 40 bases. **This rejection is maintained** for the reasons of record set forth in the previous Office Action.

Response to Arguments

In response to this rejection, Applicants argue that the specification discloses how to make and use formulations comprising liposomes that comprise a cationic lipid, phosphatidylcholine, and cholesterol, and also include an oligonucleotide that is antisense to an oncogene. Applicants contend that other oligonucleotides with sequences antisense to oncogenes are known and the art has disclosed several oligonucletoide sequences that can be used in the method described in the instant application.

Applicant's arguments have been considered but are not found persuasive because while oncogenic antisense oligonucleotides are known in the art, such oncogenic antisense oligonucleotides were not demonstrated to be effective in an improved method of treating a patient having cancerous tumor tissue, as contemplated by the instant specification.

Although the specification provides guidance to an improved method of treating a patient having cancerous tumor tissue, comprising administering a cationic liposome, phosphatidylcholine, and cholesterol, wherein the liposome has SEQ ID NO:1 encapsulated therein, the specification does not provide any evidence that any other oncogenic antisense oligonucleotide will provide such improved method of treatment. Such guidance is required since the art of antisense therapy was considered highly unpredictable at the time of filing of the instant application and the current state of the art of antisense therapy is, today, highly

unpredictable. Therefore, the skilled artisan would have to engage in undue trial and error experimentation to practice the invention as claimed in view of the many difficulties associated with antisense oligonucleotide therapy, difficulties which were apparent at the time of filing of the instant application and still apparent today.

In the previous Office Action mailed February 25, 2004, claims 9, 10, and 12-15 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of radiosensitizing tumor tissue by administration of a composition comprising a cationic liposome, phosphatidylcholine and cholesterol, and further comprising an encapsulated antisense oligonucleotide of no more than 40 bases containing SEQ ID NO:1, does not reasonably provide enablement for a method of radiosensitizing tumor tissue by administration of radiosensitizing effective amount of at least one antisense oligonucleotide of no more than 40 bases containing SEQ ID NO:1. **This rejection is maintained** for the reasons of record set forth in the previous Office Action.

Response to Arguments

In response to this rejection, Applicants argue that the claims have been amended to recite that the oligonucleotide is contained within a liposome comprising a non-toxic cationic lipid. Applicants believe this amendment to the claims obviates the instant rejection.

Applicant's arguments have been considered but are not found persuasive because the art, along with Applicants own assertions, appear to teach that phosphatidylcholine and cholesterol,

along with the oligonucleotide, are needed in concert to achieve the instant invention. For example, Gokhale et al. (Gene Therapy, 1997 Vol. 4:1289-1299) at page 1289, first column teach, "The cellular binding and uptake of oligos complexed with certain cationic liposomes have been inhibited in the presence of serum or plasma. The *in vivo* potency of antisense oligos using cationic liposomes has yet to be elucidated." Gokhale et al. also teach at page 1295, first column, "We reasoned that the presence of phosphatidylcholine should facilitate the encapsulation of oligos within the bilayered lipid vesicles. Cholesterol was included in this formulation because the presence of at least 25 mole percentage of cholesterol in liposomes has been shown to increase their stability and retention in the circulation. The phosphatidylcholine/cholesterol/DDAB liposomal formulation was found to be nontoxic, and yielded a high oligonucletoide encapsulation efficiency." Furthermore, the instant specification, at page 18, lines 12-17 teach findings that liposome encapsulation using the liposomes formulations of the invention protect the oligonucleotide from degradation. Additionally, the instant specification, at page 26, lines 1-3, discloses, "the liposomes of the invention provide significant protection of antisense oligonucleotides against degradation in blood and normal tissue". It is noted that the instant specification discloses, "the novel cationic liposomes of the invention were prepared using dimethyldiocyadecyl ammonium bromide, phosphatidylcholine and cholesterol" (see page 3, lines 12-16). Given the disclosures of the instant invention and the teachings of Gokhale et al., one of skill in the art would conclude that specific lipid formulations perform the methods as contemplated in the instant specification. Therefore, in view of applicant's admissions, in addition to teachings in the prior art, it is apparent that a composition comprising a cationic liposome, phosphatidylcholine and cholesterol, and further comprising an

encapsulated antisense oligonucleotide of no more than 40 bases containing SEQ ID NO:1 is necessary to practice the methods over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed February 25, 2004, claim 1 was rejected under 35 U.S.C. 102(b) as being anticipated by Epand et al. [U.S. Patent No. 5,283,185]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action.

Response to Arguments

In response to this rejection, Applicants argue that Epand discloses a method for facilitating the transfer of plasmids into cells that uses a mixed lipid dispersion of a cationic lipid with a co-lipid. Applicants contend that the cationic lipid of Epand "has a structure which includes a lipophilic group derived from cholesterol, a linker bond, a spacer arm, and a cationic amino group. Applicants argue that the cholesterol derivative employed by Epand are linked to a cation and thereby constitute **part of** the cationic lipid that is included with the co-lipid in the mixed lipid dispersions described therein. Applicants argue that in contrast, claim 1 recites the use of a cationic lipid, phosphatidylcholine, **and** cholesterol.

Applicant's arguments have been considered but are not found persuasive because claim 1 recites, "a composition comprising a cationic liposome comprising a cationic lipid, phosphatidylcholine, and cholesterol". The term "comprising" is open language. Therefore, the

claims are broad and do not exclude the cationic lipid of Epand, which includes a lipophilic group derived from cholesterol, wherein the cationic lipid is, for example, 3β-[N-(polyethyleneimine)-carbamoyl] cholesterol (see claim 6), a linker bond, a spacer arm, a cationic amino group, and a co-lipid of phosphatidylcholine.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
August 7, 2004

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